SPIROPYRAZOLE COMPOUNDS

This application claims priority from U.S. Provisional Application Serial No. 60/284,675, filed April 18, 2001, the disclosure of which is hereby incorporated by reference.

BACKGROUND OF THE INVENTION

Chronic pain is a major contributor to disability and is the cause of an untold amount of suffering. The successful treatment of severe and chronic pain is a primary goal of the physician with opioid analgesics being preferred drugs.

Until recently, there was evidence of three major classes of opioid receptors in the central nervous system (CNS), with each class having subtype receptors. These receptor classes were designated as μ, δ and κ. As opiates had a high affinity to these receptors while not being endogenous to the body, research followed in order to identify and isolate the endogenous ligands to these receptors. These ligands were identified as enkephalins, endorphins and dynorphins.

Recent experimentation has led to the identification of a cDNA encoding an opioid receptor-like (ORL1) receptor with a high degree of homology to the known receptor classes. This newly discovered receptor was classified as an opioid receptor based only on structural grounds, as the receptor did not exhibit pharmacological homology. It was initially demonstrated that non-selective ligands having a high affinity for μ, δ and κ receptors had low affinity for the ORL1. This characteristic, along with the fact that an endogenous ligand had not yet been discovered, led to the term "orphan receptor".

Subsequent research led to the isolation and structure of the endogenous ligand of the ORL1 receptor. This ligand is a seventeen amino acid peptide structurally similar to members of the opioid peptide family.

The discovery of the ORL1 receptor presents an opportunity in drug discovery for novel compounds which can be administered for pain management or other syndromes modulated by this receptor.

All documents cited herein, including the foregoing, are incorporated by reference in their entireties for all purposes.

OBJECTS AND SUMMARY OF THE INVENTION

It is accordingly an object of certain embodiments of the present invention to provide new compounds which exhibit affinity for the ORL1 receptor.

It is an object of certain embodiments of the present invention to provide new compounds which exhibit affinity for the ORL1 receptor and one or more of the μ, δ or κ receptors.

It is an object of certain embodiments of the present invention to provide new compounds for treating a patient suffering from chronic or acute pain by administering a compound having affinity for the ORL1 receptor.

It is an object of certain embodiments of the present invention to provide new compounds which have agonist activity at the μ, δ and κ receptors which is greater than compounds currently available e.g. morphine.

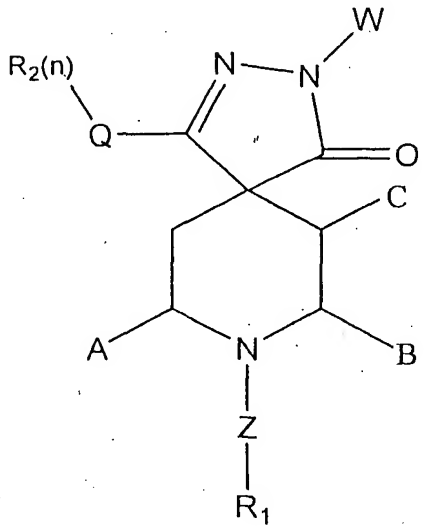
It is an object of certain embodiments of the present invention to provide methods of treating chronic and acute pain by administering compounds which have agonist activity at the μ, δ and κ receptors which is greater than compounds currently available.

It is an object of certain embodiments of the present invention to provide methods of treating chronic and acute pain by administering non-opioid compounds which have agonist activity at the μ, δ and κ receptors and which produce less side effects than compounds currently available.

It is an object of certain embodiments of the present invention to provide compounds useful as analgesics, anti-inflammatories, diuretics, anesthetics and neuroprotective agents, anti-hypertensives, anti-anxioltics; agents for appetite control; hearing regulators; anti-tussives, anti-asthmatics, modulators of locomotor activity, modulators of learning and memory, regulators of neurotransmitter and hormone release, kidney function modulators, anti-depressants, agents to treat memory loss due to Alzheimer's disease or other dementias, anti-epileptics, anti-convulsants, agents to treat withdrawal from alcohol and drugs of addiction, agents to control water balance, agents to control sodium excretion and agents to control arterial blood pressure disorders and methods for administering said compounds.

The compounds of the present invention are useful for modulating a pharmacodynamic response from one or more opioid receptors (ORL-1, μ, δ and κ) centrally and/or peripherally. The response can be attributed to the compound stimulating (agonist) or inhibiting (antagonist) the one or more receptors. Certain compounds can stimulate one receptor (e.g., a μ agonist) and inhibit a different receptor (e.g., an ORL-1 antagonist).

Other objects and advantages of the present invention will become apparent from the following detailed description thereof. The present invention in certain embodiments comprises compounds having the general formula (I):



(I)

wherein W is hydrogen, C_{1-10} alkyl, C_{3-12} cycloalkyl, C_{3-12} cycloalkylC_{1-4}alkyl-, C_{1-10} alkoxy, C_{3-12} cycloalkoxy-, C_{1-10} alkyl substituted with 1-3 halogen, C_{3-12} cycloalkyl substituted with 1-3 halogen, C_{3-12} cycloalkylC_{1-4}alkyl- substituted with 1-3 halogen, C_{1-10} alkoxy substituted with 1-3 halogen, C_{3-12} cycloalkoxy- substituted with 1-3 halogen, $-COOV_1$, $-C_{1-4}COOV_1$, $-CH_2OH$, $-SO_2N(V_1)_2$, hydroxyC_{1-10}alkyl-, hydroxyC_{3-10}cycloalkyl- , cyanoC_{1-10}alkyl-, cyanoC_{3-10}cycloalkyl-, $-CON(V_1)_2$, $NH_2SO_2C_{1-4}$alkyl-, NH_2SOC_{1-4}alkyl-, sulfonylaminoC_{1-10}alkyl-, diaminoalkyl-, -sulfonylC_{1-4}alkyl, a 6-membered heterocyclic ring, a 6-membered heteroaromatic ring, a 6-membered heterocyclicC_{1-4}alkyl-, a 6-membered

heteroaromaticC_{1-4}alkyl-, a 6-membered aromatic ring, a 6-membered aromaticC_{1-4} alkyl-, a 5-membered heterocyclic ring optionally substituted with an oxo or thio, a 5-membered heteroaromatic ring, a 5-membered heterocyclicC_{1-4}alkyl- optionally substituted with an oxo or thio, a 5-membered heteroaromaticC_{1-4}alkyl-, -C_{1-5}(=O)W_1, -C_{1-5}(=NH)W_1, -C_{1-5}NHC(=O)W_1, -C_{1-5}NHS(=O)$_2W_1$, -C_{1-5}NHS(=O)W_1, wherein W_1 is hydrogen, C_{1-10} alkyl, C_{3-12} cycloalkyl, C_{1-10} alkoxy, C_{3-12} cycloalkoxy, -CH_2OH, amino, C_{1-4}alkylamino-, diC_{1-4}alkylamino-, or a 5-membered heteroaromatic ring optionally substituted with 1-3 lower alkyl;

wherein each V_1 is independently selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl, benzyl and phenyl;

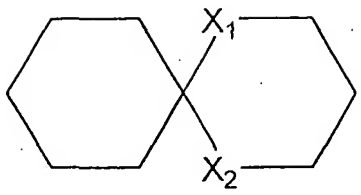
Q is a C_{1-8} alkyl, 5-8 membered cycloalkyl, 5-8 membered heterocyclic or a 6 membered aromatic or heteroaromatic group;

n is an integer from 0 to 3;

A, B and C are independently hydrogen, C_{1-10} alkyl, C_{3-12} cycloalkyl, C_{1-10} alkoxy, C_{3-12} cycloalkoxy, -CH_2OH, -$NHSO_2$, hydroxyC_{1-10}alkyl-, aminocarbonyl-, C_{1-4}alkylaminocarbonyl-, diC_{1-4}alkylaminocarbonyl-, acylamino-, acylaminoalkyl-, amide, sulfonylaminoC_{1-10}alkyl-, or A-B can together form a C_{2-6} bridge, or B-C can together form a C_{3-7} bridge, or A-C can together form a C_{1-5} bridge;

Z is selected from the group consisting of a bond, straight or branched C_{1-6} alkylene, -NH-, -CH_2O-, -CH_2NH-, -$CH_2N(CH_3)$-, -$NHCH_2$-, -CH_2CONH-, -$NHCH_2CO$-, -CH_2CO-, -$COCH_2$-, -CH_2COCH_2-, -$CH(CH_3)$-, -CH=, -O- and -HC=CH-, wherein the carbon and/or nitrogen atoms are unsubstituted or substituted with one or more lower alkyl, hydroxy, halo or alkoxy group;

R_1 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{3-12}cycloalkyl, C_{2-10}alkenyl, amino, C_{1-10}alkylamino-, C_{3-12}cycloalkylamino-, -$COOV_1$, -$C_{1-4}COOV_1$, cyano, cyanoC_{1-10}alkyl-, cyanoC_{3-10}cycloalkyl-, NH_2SO_2-, $NH_2SO_2C_{1-4}$alkyl-, NH_2SOC_{1-4}alkyl-, aminocarbonyl-, C_{1-4}alkylaminocarbonyl-, diC_{1-4}alkylaminocarbonyl-, benzyl, C_{3-12} cycloalkenyl-, a monocyclic, bicyclic or tricyclic aryl or heteroaryl ring, a hetero-monocyclic ring, a hetero-bicyclic ring system, and a spiro ring system of the formula (II):



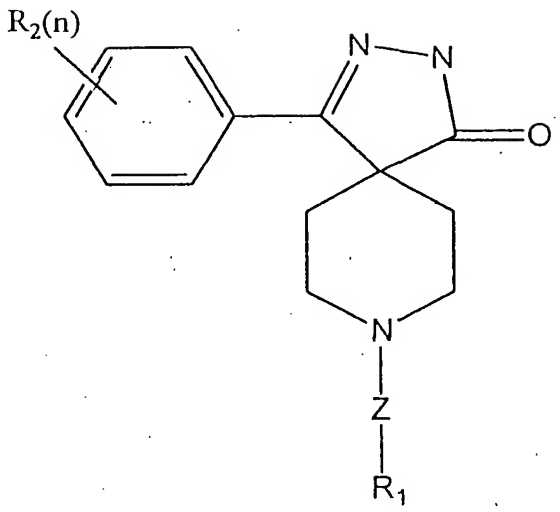
(II)

wherein X_1 and X_2 are independently selected from the group consisting of NH, O, S and CH_2; and wherein said alkyl, cycloalkyl, alkenyl, C_{1-10}alkylamino-, C_{3-12}cycloalkylamino-, or benzyl of R_1 is optionally substituted with 1-3 substituents selected from the group consisting of halogen, hydroxy, C_{1-10} alkyl, C_{1-10} alkoxy, nitro, trifluoromethyl-, cyano, -$COOV_1$, -$C_{1-4}COOV_1$, cyanoC_{1-10}alkyl-, -$C_{1-5}(=O)W_1$, -$C_{1-5}NHS(=O)_2W_1$, -$C_{1-5}NHS(=O)W_1$, a 5-membered heteroaromaticC_{0-4}alkyl-, phenyl, benzyl, benzyloxy, said phenyl, benzyl, and benzyloxy optionally being substituted with 1-3 substituents selected from the group consisting of halogen, C_{1-10} alkyl-, C_{1-10} alkoxy-, and cyano; and wherein said C_{3-12} cycloalkyl, C_{3-12} cycloalkenyl, monocyclic, bicyclic or tricyclic aryl, heteroaryl ring, hetero-monocyclic ring, hetero-bicyclic ring system, or spiro ring system of the formula (II) is optionally substituted with 1-3 substituents selected from the group consisting of halogen, C_{1-10} alkyl, C_{1-10} alkoxy, nitro, trifluoromethyl-, phenyl, benzyl, phenyloxy and benzyloxy, wherein said phenyl, benzyl, phenyloxy or benzyloxy is optionally substituted with 1-3 substituents selected from the group consisting of halogen, C_{1-10} alkyl, C_{1-10} alkoxy, and cyano;

R_2 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{3-12} cycloalkyl- and halogen, said alkyl or cycloalkyl optionally substituted with an oxo, amino, alkylamino or dialkylamino group;

and pharmaceutically acceptable salts thereof and solvates thereof.

The present invention in certain embodiments comprises compounds having the gerneral formula (IA)



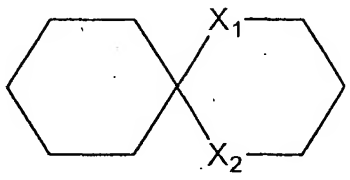
(IA)

wherein

n is an integer from 0 to 3;

Z is selected from the group consisting of a bond, -CH_2-, -NH-, -CH_2O-, -CH_2CH_2-, -CH_2NH-, -$CH_2N(CH_3)$-, -$NHCH_2$-, -CH_2CONH-, -$NHCH_2CO$-, -CH_2CO-, -$COCH_2$-, -CH_2COCH_2-, -$CH(CH_3)$-, -CH=, and -HC=CH-, wherein the carbon and/or nitrogen atoms are unsubstituted or substituted with a lower alkyl, halogen, hydroxy or alkoxy group;

R_1 is selected from the group consisting of hydrogen, C_{1-10}alkyl, C_{3-12}cycloalkyl, C_{2-10}alkenyl, amino, C_{1-10}alkylamino, C_{3-12}cycloalkylamino, benzyl, C_{3-12} cycloalkenyl, a monocyclic, bicyclic or tricyclic aryl or heteroaryl ring, a hetero-monocyclic ring, a hetero-bicyclic ring system, and a spiro ring system of the formula (II):



(II)

wherein X_1 and X_2 are independently selected from the group consisting of NH, O, S and CH_2;

wherein said monocyclic aryl is preferably phenyl;

wherein said bicyclic aryl is preferably naphthyl;

wherein said alkyl, cycloalkyl, alkenyl, C_{1-10}alkylamino, C_{3-12}cycloalkylamino, or benzyl is optionally substituted with 1-3 substituents selected from the group consisting of halogen, C_{1-10} alkyl, C_{1-10} alkoxy, nitro, trifluoromethyl, cyano, phenyl, benzyl, benzyloxy, said phenyl, benzyl, and benzyloxy optionally being substituted with 1-3 substituents selected from the group consisting of halogen, C_{1-10} alkyl, C_{1-10} alkoxy, and cyano;

wherein said C_{3-12} cycloalkyl, C_{3-12} cycloalkenyl, monocyclic, bicyclic or tricyclic aryl, heteroaryl ring, hetero-monocyclic ring, hetero-bicyclic ring system, and spiro ring system of the formula (II) are optionally substituted with 1-3 substituents selected from the group consisting of halogen, C_{1-10} alkyl, C_{1-10} alkoxy, nitro, trifluoromethyl, phenyl, benzyl, phenyloxy and benzyloxy, wherein said phenyl, benzyl, phenyloxy and benzyloxy are optionally substituted with 1-3 substituents selected from the group consisting of halogen, C_{1-10} alkyl, C_{1-10} alkoxy, and cyano;

R_2 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{3-12} cycloalkyl and halogen, said alkyl optionally substituted with an oxo group;

and pharmaceutically acceptable salts thereof and solvates thereof.

In certain preferred embodiments of formula (I), Q is phenyl or a 6 membered heteroaromatic group containing 1-3 nitrogen atoms.

In certain preferred embodiments of formula (I) or (IA), the R_1 alkyl is methyl, ethyl, propyl, butyl, pentyl, or hexyl.

In certain preferred embodiments of formula (I) or (IA), the R_1 cycloalkyl is cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, or norbornyl.

In other preferred embodiments of formula (I) or (IA), the R_1 bicyclic ring system is naphthyl. In other preferred embodiments of formula (I) or (IA), the R_1 bicyclic ring system is tetrahydronaphthyl, or decahydronaphthyl and the R_1 tricyclic ring system is dibenzocycloheptyl. In other preferred embodiments R_1 is phenyl or benzyl.

In other preferred embodiments of formula (I) or (IA), the R_1 bicyclic aromatic ring is a 10-membered ring, preferably quinoline or naphthyl.

In other preferred embodiments of formula (I) or (IA), the R_1 bicyclic aromatic ring is a 9-membered ring, preferably indenyl.

In certain embodiments of formula (I) or (IA), Z is a bond, methyl, or ethyl.

In certain embodiments of formula (I) or (IA), the Z group is maximally substituted as not to have any hydrogen substitution on the base Z group. For example, if the base Z group is $-CH_2-$, substitution with two methyl groups would remove hydrogens from the $-CH_2-$ base Z group.

In other preferred embodiments of formula (I) or (IA), n is 0.

In certain embodiments of formula (I) or (IA), X_1 and X_2 are both O.

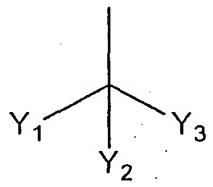
In certain embodiments of formula (I), W is $-CH_2C=ONH_2$, $-C(NH)NH_2$, pyridylmethyl, cyclopentyl, cyclohexyl, furanylmethyl, $-C=OCH_3$, $-CH_2CH_2NHC=OCH_3$, $-SO_2CH_3$, $CH_2CH_2NHSO_2CH_3$, furanylcarbonyl-, methylpyrrolylcarbonyl-, diazolecarbonyl-, azolemethyl-, trifluoroethyl-, hydroxyethyl-, cyanomethyl-, oxo-oxazolemethyl-, or diazolemethyl-.

In certain embodiments of formula (I), ZR_1 is cyclohexylethyl-, cyclohexylmethyl-, cyclopentylmethyl-, dimethylcyclohexylmethyl-, phenylethyl-, pyrrolyltrifluoroethyl-, thienyltrifluoroethyl-, pyridylethyl-, cyclopentyl-, cyclohexyl-, methoxycyclohexyl-, tetrahydropyranyl-, propylpiperidinyl-, indolylmethyl-, pyrazoylpentyl-, thiazolylethyl-, phenyltrifluoroethyl-, hydroxyhexyl-, methoxyhexyl-, isopropoxybutyl-, hexyl-, or oxocanylpropyl-.

In certain embodiments of formula (I), at least one of ZR_1 or W is $-CH_2COOV_1$, tetrazolylmethyl-, cyanomethyl-, NH_2SO_2methyl-, NH_2SOmethyl-, aminocarbonylmethyl-, C_{1-4}alkylaminocarbonylmethyl-, or diC_{1-4}alkylaminocarbonylmethyl-.

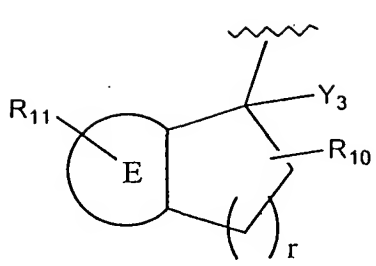
In certain embodiments of formula (I), ZR_1 is 3,3 diphenylpropyl optionally substituted at the 3 carbon of the propyl with $-COOV_1$, tetrazolylC_{0-4}alkyl-, cyano-, aminocarbonyl-, C_{1-4}alkylaminocarbonyl-, or diC_{1-4}alkylaminocarbonyl-.

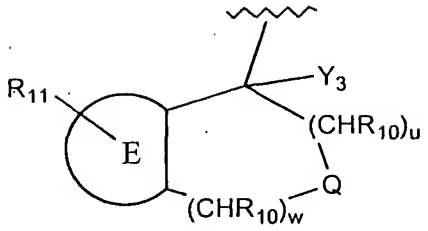
In alternate embodiments of formula (I) or (IA), ZR_1 can be

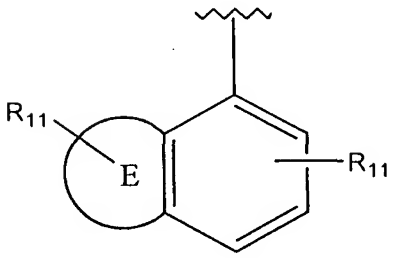


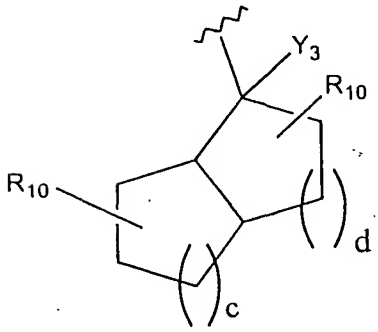
wherein

Y_1 is R_3-(C_1-C_{12})alkyl, R_4-aryl, R_5-heteroaryl, R_6-(C_3-C_{12})cyclo-alkyl, R_7-(C_3-C_7)heterocycloalkyl, $-CO_2$(C_1-C_6)alkyl, CN or $-C(O)NR_8R_9$; Y_2 is hydrogen or Y_1; Y_3 is hydrogen or (C_1-C_6)alkyl; or Y_1, Y_2 and Y_3, together with the carbon to which they are attached, form one of the following structures:









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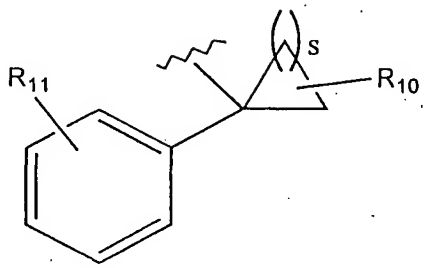


wherein r is 0 to 3; w and u are each 0-3, provided that the sum of w and u is 1-3; c and d are independently 1 or 2; s is 1 to 5; and ring E is a fused R_4-phenyl or R_5-heteroaryl ring;

R_{10} is 1 to 3 substituents independently selected from the group consisting of H, $(C_1$-$C_6)$alkyl, $-OR_8$, $-(C_1$-$C_6)$alkyl-OR_8, $-NR_8R_9$ and $-(C_1$-$C_6)$alkyl-NR_8R_9;

R_{11} is 1 to 3 substituents independently selected from the group consisting of R_{10}, $-CF_3$, $-OCF_3$, NO_2 and halo, or R_{11} substituents on adjacent ring carbon atoms may together form a methylenedioxy or ethylenedioxy ring;

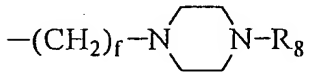
R_8 and R_9 are independently selected from the group consisting of hydrogen, $(C_1$-$C_6)$ alkyl, $(C_3$-$C_{12})$cycloalkyl, aryl and aryl$(C_1$-$C_6)$alkyl;

R_3 is 1 to 3 substituents independently selected from the group consisting of H, R_4-aryl, R_6-$(C_3$-$C_{12})$cycloalkyl, R_5-heteroaryl, R_7-$(C_3$-$C_7)$heterocycloalkyl, $-NR_8R_9$, $-OR_{12}$ and $-S(O)_{0\text{-}2}R_{12}$;

R_6 is 1 to 3 substituents independently selected from the group consisting of H,

(C_1-C_6)alkyl, R_4-aryl, -NR_8R_9 , -OR_{12} and -SR_{12};

R_4 is 1 to 3 substituents independently selected from the group consisting of hydrogen, halo, (C_1- C_6)alkyl, R_{13}-aryl, (C_3 - C_{12})cycloalkyl, -CN, -CF_3, -OR_8, -(C_1-C_6)alkyl-OR_8, -OCF_3, -NR_8R_9, -(C_1 - C_6)alkyl -NR_8R_9, -$NHSO_2R_8$, -$SO_2N(R_{14})_2$, -SO_2R_8, -SOR_8, -SR_8, -NO_2, -$CONR_8R_9$, -NR_9COR_8, -COR_8, -$COCF_3$, -$OCOR_8$, -OCO_2R_8, -$COOR_8$, -(C_1-C_6)alkyl-$NHCOOC(CH_3)_3$, -(C_1-C_6)alkyl-$NHCOCF_3$, -(C_1-C_6)alkyl-$NHSO_2$-(C_1-C_6)alkyl, -(C_1-C_6)alkyl-NHCONH-(C_1-C_6)-alkyl and



wherein f is 0 to 6; or R_4 substituents on adjacent ring carbon atoms may together form a methylenedioxy or ethylenedioxy ring;

R_5 is 1 to 3 substituents independently selected from the group consisting of hydrogen, halo, (C_1-C_6)alkyl, R_{13}-aryl, (C_3-C_{12})cycloalkyl, -CN, -CF_3, -OR_8, -(C_1-C_6)alkyl-OR_8, -OCF_3,-NR_8R_9, -(C_1-C_6)alkyl-NR_8R_9, -$NHSO_2R_8$, -$SO_2N(R_{14})_2$, -NO_2, -$CONR_8R_9$, -NR_9COR_8, -COR_8, -$OCOR_8$, -OCO_2R_8 and -$COOR_8$;

R_7 is H, (C_1-C_6)alkyl, -OR_8, -(C_1-C_6)alkyl-OR_8, -NR_8R_9 or -(C_1-C_6)alkyl-NR_8R_9;

R_{12} is H, (C_1-C_6)alkyl, R_4-aryl, -(C_1-C_6)alkyl-OR_8, -(C_1-C_6)alkyl-NR_8R_9, -(C_1-C_6)alkyl-SR_8, or aryl (C_1-C_6)alkyl;

R_{13} is 1-3 substituents independently selected from the group consisting of H, (C_1-C_6)alkyl, (C_1-C_6)alkoxy and halo;

R_{14} is independently selected from the group consisting of H, (C_1-C_6)alkyl and R_{13}-C_6H_4-CH_2-.

As used herein, the term "alkyl" means a linear or branched saturated aliphatic hydrocarbon group having a single radical and 1-10 carbon atoms. Examples of alkyl groups include methyl, propyl, isopropyl, butyl, n-butyl, isobutyl, sec-butyl, tert-butyl, and pentyl.. A branched alkyl means that one or more alkyl groups such as methyl, ethyl or propyl, replace one or both hydrogens in a -CH_2- group of a linear alkyl chain. The term "lower alkyl" means an alkyl of 1-3 carbon atoms.

The term "alkoxy" means an "alkyl" as defined above connected to an oxygen radical.

The term "cycloalkyl" means a non-aromatic mono- or multicyclic hydrocarbon ring system having a single radical and 3-12 carbon atoms. Exemplary monocyclic cycloalkyl rings include cyclopropyl, cyclopentyl, and cyclohexyl. Exemplary multicyclic cycloalkyl rings include adamantyl and norbornyl.

The term "alkenyl" means a linear or branched aliphatic hydrocarbon group containing a carbon-carbon double bond having a single radical and 2-10 carbon atoms.

A "branched" alkenyl means that one or more alkyl groups such as methyl, ethyl or propyl replace one or both hydrogens in a $-CH_2-$ or -CH= linear alkenyl chain. Exemplary alkenyl groups include ethenyl, 1- and 2- propenyl, 1-, 2- and 3- butenyl, 3-methylbut-2-enyl, 2-propenyl, heptenyl, octenyl and decenyl.

The term "cycloalkenyl" means a non-aromatic monocyclic or multicyclic hydrocarbon ring system containing a carbon-carbon double bond having a single radical and 3 to 12 carbon atoms. Exemplary monocyclic cycloalkenyl rings include cyclopropenyl, cyclopentenyl, cyclohexenyl or cycloheptenyl. An exemplary multicyclic cycloalkenyl ring is norbornenyl.

The term "aryl" means a carbocyclic aromatic ring system containing one, two or three rings which may be attached together in a pendent manner or fused, and containing a single radical. Exemplary aryl groups include phenyl, naphthyl and acenaphthyl.

The term "heterocyclic" means cyclic compounds having one or more heteroatoms (atoms other than carbon) in the ring, and having a single radical. The ring may be saturated, partially saturated or unsaturated, and the heteroatoms may be selected from the group consisting of nitrogen, sulfur and oxygen. Examples of saturated heterocyclic radicals include saturated 3 to 6- membered hetero-monocyclic groups containing 1 to 4 nitrogen atoms, such as pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl; saturated 3- to 6- membered hetero-monocyclic groups containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, such as morpholinyl; saturated 3- to 6- membered hetero-monocyclic groups containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, such as thiazolidinyl. Examples of partially saturated heterocyclic radicals include dihydrothiophene, dihydropyran, and dihydrofuran. Other heterocyclic groups can be 7 to 10 carbon rings substituted with heteroatoms such as oxocanyl and thiocanyl. When the heteroatom is sulfur, the sulfur can be a sulfur dioxide such as thiocanyldioxide.

The term "heteroaryl" means unsaturated heterocyclic radicals, wherein "heterocyclic" is as previously described. Exemplary heteroaryl groups include unsaturated 3 to 6 membered hetero-monocyclic groups containing 1 to 4 nitrogen atoms, such as pyrrolyl, pyridyl, pyrimidyl, and pyrazinyl; unsaturated condensed heterocyclic groups containing 1 to 5 nitrogen atoms, such as indolyl, quinolyl and isoquinolyl; unsaturated 3 to 6- membered hetero-monocyclic groups containing an oxygen atom, such as furyl; unsaturated 3 to 6 membered hetero-monocyclic groups containing a sulfur atom,

such as thienyl; unsaturated 3 to 6 membered hetero-monocyclic groups containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, such as oxazolyl; unsaturated condensed heterocyclic groups containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, such as benzoxazolyl; unsaturated 3 to 6 membered hetero-monocyclic groups containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, such as thiazolyl; and unsaturated condensed heterocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, such as benzothiazolyl. The term "heteroaryl" also includes unsaturated heterocyclic radicals, wherein "heterocyclic" is as previously described, in which the heterocyclic group is fused with an aryl group, in which aryl is as previously described. Exemplary fused radicals include benzofuran, benzdioxole and benzothiophene.

As used herein, the term "heterocyclicC_{1-4}alkyl", "heteroaromaticC_{1-4}alkyl" and the like refer to the ring structure bonded to a C_{1-4} alkyl radical.

All of the cyclic ring structures disclosed herein can be attached at any point where such connection is possible, as recognized by one skilled in the art.

As used herein, the term "patient" includes a human or an animal such as a companion animal or livestock.

As used herein, the term "halogen" includes fluoride, bromide, chloride, iodide or alabamide.

The invention disclosed herein is meant to encompass all pharmaceutically acceptable salts thereof of the disclosed compounds. The pharmaceutically acceptable salts include, but are not limited to, metal salts such as sodium salt, potassium salt, cesium salt and the like; alkaline earth metals such as calcium salt, magnesium salt and the like; organic amine salts such as triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt and the like; inorganic acid salts such as hydrochloride, hydrobromide, sulfate, phosphate and the like; organic acid salts such as formate, acetate, trifluoroacetate, maleate, fumarate, tartrate and the like; sulfonates such as methanesulfonate, benzenesulfonate, p-toluenesulfonate, and the like; amino acid salts such as arginate, asparginate, glutamate and the like.

The invention disclosed herein is also meant to encompass all prodrugs of the disclosed compounds. Prodrugs are considered to be any covalently bonded carriers which release the active parent drug in vivo.

The invention disclosed herein is also meant to encompass the in vivo metabolic products of the disclosed compounds. Such products may result for example from the oxidation, reduction, hydrolysis, amidation, esterification and the like of the administered

compound, primarily due to enzymatic processes. Accordingly, the invention includes compounds produced by a process comprising contacting a compound of this invention with a mammal for a period of time sufficient to yield a metabolic product thereof. Such products typically are identified by preparing a radiolabelled compound of the invention, administering it parenterally in a detectable dose to an animal such as rat, mouse, guinea pig, monkey, or to man, allowing sufficient time for metabolism to occur and isolating its conversion products from the urine, blood or other biological samples.

The invention disclosed herein is also meant to encompass the disclosed compounds being isotopically-labelled by having one or more atoms replaced by an atom having a different atomic mass or mass number. Examples of isotopes that can be incorporated into the disclosed compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively. Some of the compounds disclosed herein may contain one or more asymmetric centers and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms. The present invention is also meant to encompass all such possible forms as well as their racemic and resolved forms and mixtures thereof. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended to include both E and Z geometric isomers. All tautomers are intended to be encompassed by the present invention as well

As used herein, the term "stereoisomers" is a general term for all isomers of individual molecules that differ only in the orientation of their atoms in space. It includes enantiomers and isomers of compounds with more than one chiral center that are not mirror images of one another (diastereomers).

The term "chiral center" refers to a carbon atom to which four different groups are attached.

The term "enantiomer" or "enantiomeric" refers to a molecule that is nonsuperimposeable on its mirror image and hence optically active wherein the enantiomer rotates the plane of polarized light in one direction and its mirror image rotates the plane of polarized light in the opposite direction.

The term "racemic" refers to a mixture of equal parts of enantiomers and which is optically inactive.

The term "resolution" refers to the separation or concentration or depletion of one of the two enantiomeric forms of a molecule.

The term "modulate" as used herein with respect to the ORL-1 receptor means the mediation of a pharmacodynamic response (e.g., analgesia) in a subject from (i) inhibiting or activating the receptor, or (ii) directly or indirectly affecting the normal regulation of the receptor activity. Compounds which modulate the receptor activity include agonists,

antagonists, mixed agonists/antagonists and compounds which directly or indirectly affect regulation of the receptor activity.

Certain preferred compounds of the invention include:

8-(4-propylcyclohexyl)-1-phenyl-2,3,8-triazospiro[4.5]decan-4-one;

8-(5-methylhex-2-yl)-1-phenyl-2,3,8-triazospiro[4.5]decan-4-one;

8-norbornyl-1-phenyl-2,3,8-triazospiro[4.5]decan-4-one;

8-(decahydro-2-naphthyl)-1-phenyl-2,3,8-triazospiro[4.5]decan-4-one;

8-(cyclooctylmethyl)-1-phenyl-2,3,8-triazospiro[4.5]decan-4-one;

8-(1,2,3,4-tetrahydro-2-naphthyl)-1-phenyl-2,3,8-triazospiro[4.5]decan-4-one;

8-[4-(2-propyl)-cyclohexyl]-1-phenyl-2,3,8-triazospiro[4.5]decan-4-one;

8-(1,3-dihydroinden-2-yl)-1-phenyl-2,3,8-triazospiro[4.5]decan-4-one;

8-[(naphth-2-yl-methyl)]-1-phenyl-2,3,8-triazospiro[4.5]decan-4-one;

8-(*p*-phenylbenzyl)-1-phenyl-2,3,8-triazospiro[4.5]decan-4-one;

8-[4,4-Bis(4-fluorophenyl)butyl]-1-phenyl-2,3,8-triazospiro[4.5]decan-4-one;

8-(benzyl)-1-phenyl-2,3,8-triazospiro[4.5]decan-4-one;

8-(10,11-Dihydro-5H-dibenzo[a,d]-cyclohepten-5-yl)-1-phenyl-2,3,8-triazospiro[4.5]decan-4-one;

8-(3,3-Bis(phenyl)propyl)-1-phenyl-2,3,8-triazospiro[4.5]decan-4-one;

8-(*p*-benzyloxybenzyl)-1-phenyl-2,3,8-triazospiro[4.5]decan-4-one;

8-(cyclooctylmethyl)-1-phenyl-2,3,8-triazospiro[4.5]decan-4-one; and

pharmaceutically acceptable salts thereof and solvates thereof.

Another preferred compound is 8-(acenaphthen-9-yl)-1-phenyl-2,3,8-triazospiro[4.5]decan-4-one and pharmaceutically acceptable salts thereof and solvates thereof.

The present invention also provides use of any of the disclosed compounds in the preparation of a medicament for treating pain and other disease states modulated by an opioid receptor, e.g., the ORL-1 receptor.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of the present invention can be administered to anyone requiring modulation of the opioid and ORL1 receptors. Administration may be orally, topically, by suppository, inhalation, or parenterally.

The present invention also encompasses all pharmaceutically acceptable salts of the foregoing compounds. One skilled in the art will recognize that acid addition salts of the presently claimed compounds may be prepared by reaction of the compounds with the appropriate acid via a variety of known methods.

Various oral dosage forms can be used, including such solid forms as tablets, gelcaps, capsules, caplets, granules, lozenges and bulk powders and liquid forms such as

emulsions, solution and suspensions. The compounds of the present invention can be administered alone or can be combined with various pharmaceutically acceptable carriers and excipients known to those skilled in the art, including but not limited to diluents, suspending agents, solubilizers, binders, disintegrants, preservatives, coloring agents, lubricants and the like.

When the compounds of the present invention are incorporated into oral tablets, such tablets can be compressed, tablet triturates, enteric-coated, sugar-coated, film-coated, multiply compressed or multiply layered. Liquid oral dosage forms include aqueous and nonaqueous solutions, emulsions, suspensions, and solutions and/or suspensions reconstituted from non-effervescent granules, containing suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, coloring agents, and flavoring agents. When the compounds of the present invention are to be injected parenterally, they may be, e.g., in the form of an isotonic sterile solution. Alternatively, when the compounds of the present invention are to be inhaled, they may be formulated into a dry aerosol or may be formulated into an aqueous or partially aqueous solution.

In addition, when the compounds of the present invention are incorporated into oral dosage forms, it is contemplated that such dosage forms may provide an immediate release of the compound in the gastrointestinal tract, or alternatively may provide a controlled and/or sustained release through the gastrointestinal tract. A wide variety of controlled and/or sustained release formulations are well known to those skilled in the art, and are contemplated for use in connection with the formulations of the present invention. The controlled and/or sustained release may be provided by, e.g., a coating on the oral dosage form or by incorporating the compound(s) of the invention into a controlled and/or sustained release matrix.

Specific examples of pharmaceutically acceptable carriers and excipients that may be used to formulate oral dosage forms, are described in the Handbook of Pharmaceutical Excipients, American Pharmaceutical Association (1986). Techniques and compositions for making solid oral dosage forms are described in Pharmaceutical Dosage Forms: Tablets (Lieberman, Lachman and Schwartz, editors) 2nd edition, published by Marcel Dekker, Inc. Techniques and compositions for making tablets (compressed and molded), capsules (hard and soft gelatin) and pills are also described in Remington's Pharmaceutical Sciences (Arthur Osol, editor), 1553B1593 (1980). Techniques and composition for making liquid oral dosage forms are described in Pharmaceutical Dosage Forms: Disperse Systems, (Lieberman, Rieger and Banker, editors) published by Marcel Dekker, Inc.

When the compounds of the present invention are incorporated for parenteral administration by injection (e.g., continuous infusion or bolus injection), the formulation for parenteral administration may be in the form of suspensions, solutions, emulsions in oily or aqueous vehicles, and such formulations may further comprise pharmaceutically

necessary additives such as stabilizing agents, suspending agents, dispersing agents, and the like. The compounds of the invention may also be in the form of a powder for reconstitution as an injectable formulation.

In certain embodiments, the compounds of the present invention can be used in combination with at least one other therapeutic agent. Therapeutic agents include, but are not limited to, μ-opioid agonists; non-opioid analgesics; non-steroid antiinflammatory agents; Cox-II inhibitors; antiemetics; β-adrenergic blockers; anticonvulsants; antidepressants; Ca2+-channel blockers; anticancer agent and mixtures thereof.

In certain embodiments, the compounds of the present invention can be formulated in a pharmaceutical dosage form in combination with a μ-opioid agonist. μ-opioid agonists, which may be included in the formulations of the present invention include but are not limited to include alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, desomorphine, dextromoramide, dezocine, diampromide, diamorphone, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, nalbuphine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, proheptazine, promedol, properidine, propiram, propoxyphene, sufentanil, tilidine, tramadol, pharmaceutically acceptable salts thereof, and mixtures thereof.

In certain preferred embodiments, the μ-opioid agonist is selected from codeine, hydromorphone, hydrocodone, oxycodone, dihydrocodeine, dihydromorphine, morphine, tramadol, oxymorphone, pharmaceutically acceptable salts thereof, and mixtures thereof.

In another embodiment of the invention, the medicament comprises a mixture of a Cox-II inhibitor and an inhibitor of 5-lipoxygenase for the treatment of pain and/or inflammation. Suitable Cox-II inhibitors and 5-lipoxygenase inhibitors, as well as combinations thereof are described in U.S. Patent No. 6,136,839, which is hereby incorporated by reference in its entirety. Cox-II inhibitors include, but are not limited to rofecoxib (Vioxx), celecoxib (Celebrex), DUP-697, flosulide, meloxicam, 6-MNA, L-745337, nabumetone, nimesulide, NS-398, SC-5766, T-614, L-768277, GR-253035, JTE-522, RS-57067-000, SC-58125, SC-078, PD-138387, NS-398, flosulide, D-1367, SC-

5766, PD-164387, etoricoxib, valdecoxib and parecoxib or pharmaceutically acceptable salts, enantiomers or tautomers thereof.

The compounds of the present invention can also be combined in dosage forms with non-opioid analgesics, e.g., non-steroidal anti-inflammatory agents, including aspirin, ibuprofen, diclofenac, naproxen, benoxaprofen, flurbiprofen, fenoprofen, flubufen, ketoprofen, indoprofen, piroprofen, carprofen, oxaprozin, pramoprofen, muroprofen, trioxaprofen, suprofen, aminoprofen, tiaprofenic acid, fluprofen, bucloxic acid, indomethacin, sulindac, tolmetin, zomepirac, tiopinac, zidometacin, acemetacin, fentiazac, clidanac, oxpinac, mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid tolfenamic acid, diflurisal, flufenisal, piroxicam, sudoxicam or isoxicam, pharmaceutically acceptable salts thereof, and mixtures thereof. Other suitable non-opioid analgesics which may be included in the dosage forms of the present invention include the following, non-limiting, chemical classes of analgesic, antipyretic, nonsteroidal antifinflammatory drugs: salicylic acid derivatives, including aspirin, sodium salicylate, choline magnesium trisalicylate, salsalate, diflunisal, salicylsalicylic acid, sulfasalazine, and olsalazin; para-aminophennol derivatives including acetaminophen; indole and indene acetic acids, including indomethacin, sulindac, and etodolac; heteroaryl acetic acids, including tolmetin, diclofenac, and ketorolac; anthranilic acids (fenamates), including mefenamic acid, and meclofenamic acid; enolic acids, including oxicams (piroxicam, tenoxicam), and pyrazolidinediones (phenylbutazone, oxyphenthartazone); and alkanones, including nabumetone. For a more detailed description of the NSAIDs that may be included within the medicaments employed in the present invention, see Paul A. Insel Analgesic-Antipyretic and Antiinflammatory Agents and Drugs Employed in the treatment of Gout in Goodman & Gilman's The Pharmacological Basis of Therapeutics, 617-57 (Perry B. Molinhoff and Raymond W. Ruddon, Eds., Ninth Edition, 1996), and Glen R. Hanson Analgesic, Antipyretic and Anit-Inflammatory Drugs in Remington: The Science and Practice of Pharmacy Vol II, 1196-1221 (A. R. Gennaro, Ed. 19th Ed. 1995) which are hereby incorporated by reference in their entireties.

In certain embodiments, the compounds of the present invention can be formulated in a pharmaceutical dosage form in combination with antimigraine agents. Antimigraine agents include, but are not limited to, alpiropride, dihydroergotamine, dolasetron, ergocornine, ergocorninine, ergocryptine, ergot, ergotamine, flumedroxone acetate,fonazine,lisuride, lomerizine, methysergide oxetorone, pizotyline, and mixtures thereof.

The other therapeutic agent can also be an adjuvant to reduce any potential side effects such as, for example, an antiemetic agent. Suitable antiemetic agents include, but are not limited to, metoclopromide, domperidone, prochlorperazine, promethazine, chlorpromazine, trimethobenzamide, ondansetron, granisetron, hydroxyzine, acethylleucine monoethanolamine, alizapride, azasetron, benzquinamide, bietanautine, bromopride, buclizine, clebopride, cyclizine, dimenhydrinate, diphenidol, dolasetron, meclizine, methallatal, metopimazine, nabilone, oxyperndyl, pipamazine, scopolamine, sulpiride, tetrahydrocannabinols, thiethylperazine, thioproperazine, tropisetron, and mixtures thereof.

In certain embodiments, the compounds of the present invention can be formulated in a pharmaceutical dosage form in combination with β-adrenergic blockers. Suitable β-adrenergic blockers include, but are not limited to, acebutolol, alprenolol, amosulabol, arotinolol, atenolol, befunolol, betaxolol, bevantolol, bisoprolol, bopindolol, bucumolol, bufetolol, bufuralol, bunitrolol, bupranolol, butidrine hydrochloride, butofilolol, carazolol, carteolol, carvedilol, celiprolol, cetamolol, cloranolol, dilevalol, epanolol, esmolol, indenolol, labetalol, levobunolol, mepindolol, metipranolol, metoprolol, moprolol, nadolol, nadoxolol, nebivalol, nifenalol, nipradilol, oxprenolol, penbutolol, pindolol, practolol, pronethalol, propranolol, sotalol, sulfinalol, talinolol, tertatolol, tilisolol, timolol, toliprolol, and xibenolol.

In certain embodiments, the compounds of the present invention can be formulated in a pharmaceutical dosage form in combination with anticonvulsants. Suitable anticonvulsants include, but are not limited to, acetylpheneturide, albutoin, aloxidone, aminoglutethimide, 4-amino-3-hydroxybutyric acid, atrolactamide,beclamide, buramate, calcium bromide, carbamazepine, cinromide, clomethiazole, clonazepam, decimemide, diethadione, dimethadione, doxenitroin, eterobarb, ethadione, ethosuximide, ethotoin, felbamate, fluoresone, gabapentin, 5-hydroxytryptophan, lamotrigine, magnesium bromide, magnesium sulfate, mephenytoin, mephobarbital, metharbital, methetoin, methsuximide, 5-methyl-5-(3-phenanthryl)-hydantoin, 3-methyl-5-phenylhydantoin, narcobarbital, nimetazepam, nitrazepam, oxcarbazepine, paramethadione, phenacemide, phenetharbital, pheneturide, phenobarbital, phensuximide, phenylmethylbarbituric acid, phenytoin, phethenylate sodium, potassium bromide, pregabaline, primidone, progabide, sodium bromide, solanum, strontium bromide, suclofenide, sulthiame, tetrantoin, tiagabine, topiramate, trimethadione, valproic acid, valpromide, vigabatrin, and zonisamide.

In certain embodiments, the compounds of the present invention can be formulated in a pharmaceutical dosage form in combination with antidepressants. Suitable

antidepressants include, but are not limited to, binedaline, caroxazone, citalopram, dimethazan, fencamine, indalpine, indeloxazine hydrocholoride, nefopam, nomifensine, oxitriptan, oxypertine, paroxetine, sertraline, thiazesim, trazodone, benmoxine, iproclozide, iproniazid, isocarboxazid, nialamide, octamoxin, phenelzine, cotinine, rolicyprine, rolipram, maprotiline, metralindole, mianserin, mirtazepine, adinazolam, amitriptyline, amitriptylinoxide, amoxapine, butriptyline, clomipramine, demexiptiline, desipramine, dibenzepin, dimetacrine, dothiepin, doxepin, fluacizine, imipramine, imipramine N-oxide, iprindole, lofepramine, melitracen, metapramine, nortriptyline, noxiptilin, opipramol, pizotyline, propizepine, protriptyline, quinupramine, tianeptine, trimipramine, adrafinil, benactyzine, bupropion, butacetin, dioxadrol, duloxetine, etoperidone, febarbamate, femoxetine, fenpentadiol, fluoxetine, fluvoxamine, hematoporphyrin, hypericin, levophacetoperane, medifoxamine, milnacipran, minaprine, moclobemide, nefazodone, oxaflozane, piberaline, prolintane, pyrisuccideanol, ritanserin, roxindole, rubidium chloride, sulpiride, tandospirone, thozalinone, tofenacin, toloxatone, tranylcypromine, L-tryptophan, venlafaxine, viloxazine, and zimeldine.

In certain embodiments, the compounds of the present invention can be formulated in a pharmaceutical dosage form in combination with Ca2+-channel blockers. Suitable Ca2+-channel blockers include, but are not limited to, bepridil, clentiazem, diltiazem, fendiline, gallopamil, mibefradil, prenylamine, semotiadil, terodiline, verapamil, amlodipine, aranidipine, barnidipine, benidipine, cilnidipine, efonidipine, elgodipine, felodipine, isradipine, lacidipine, lercanidipine, manidipine, nicardipine, nifedipine, nilvadipine, nimodipine, nisoldipine, nitrendipine, cinnarizine, flunarizine, lidoflazine, lomerizine, bencyclane, etafenone, fantofarone, and perhexiline.

In certain embodiments, the compounds of the present invention can be formulated in a pharmaceutical dosage form in combination with anticancer agents. Suitable anticancer agents include, but are not limited to, acivicin; aclarubicin; acodazole hydrochloride; acronine; adozelesin; aldesleukin; altretamine; ambomycin; ametantrone acetate; aminoglutethimide; amsacrine; anastrozole; anthramycin; asparaginase; asperlin; azacitidine; azetepa; azotomycin; batimastat; benzodepa; bicalutamide; bisantrene hydrochloride; bisnafide dimesylate; bizelesin; bleomycin sulfate; brequinar sodium; bropirimine; busulfan; cactinomycin; calusterone; caracemide; carbetimer; carboplatin; carmustine; carubicin hydrochloride; carzelesin; cedefingol; chlorambucil; cirolemycin; cisplatin; cladribine; crisnatol mesylate; cyclophosphamide; cytarabine; dacarbazine; dactinomycin; daunorubicin hydrochloride; decitabine; dexormaplatin; dezaguanine;

dezaguanine mesylate; diaziquone; docetaxel; doxorubicin; doxorubicin hydrochloride; droloxifene; droloxifene citrate; dromostanolone propionate; duazomycin; edatrexate; eflornithine hydrochloride; elsamitrucin; enloplatin; enpromate; epipropidine; epirubicin hydrochloride; erbulozole; esorubicin hydrochloride; estramustine; estramustine phosphate sodium; etanidazole; etoposide; etoposide phosphate; etoprine; fadrozole hydrochloride; fazarabine; fenretinide; floxuridine; fludarabine phosphate; fluorouracil; flurocitabine; fosquidone; fostriecin sodium; gemcitabine; gemcitabine hydrochloride; hydroxyurea; idarubicin hydrochloride; ifosfamide; ilmofosine; interleukin II (including recombinant interleukin II, or rIL2), interferon alfa-2a; interferon alfa-2b; interferon alfa-n1 ; interferon alfa-n3; interferon beta-I a; interferon gamma-I b; iproplatin; irinotecan hydrochloride; lanreotide acetate; letrozole; leuprolide acetate; liarozole hydrochloride; lometrexol sodium; lomustine; losoxantrone hydrochloride; masoprocol; maytansine; mechlorethamine hydrochloride; megestrol acetate; melengestrol acetate; melphalan; menogaril; mercaptopurine; methotrexate; methotrexate sodium; metoprine; meturedepa; mitindomide; mitocarcin; mitocromin; mitogillin; mitomalcin; mitomycin; mitosper; mitotane; mitoxantrone hydrochloride; mycophenolic acid; nocodazole; nogalamycin; ormaplatin; oxisuran; paclitaxel; pegaspargase; peliomycin; pentamustine; peplomycin sulfate; perfosfamide; pipobroman; piposulfan; piroxantrone hydrochloride; plicamycin; plomestane; porfimer sodium; porfiromycin; prednimustine; procarbazine hydrochloride; puromycin; puromycin hydrochloride; pyrazofurin; riboprine; rogletimide; safingol; safingol hydrochloride; semustine; simtrazene; sparfosate sodium; sparsomycin; spirogermanium hydrochloride; spiromustine; spiroplatin; streptonigrin; streptozocin; sulofenur; talisomycin; tecogalan sodium; tegafur; teloxantrone hydrochloride; temoporfin; teniposide; teroxirone; testolactone; thiamiprine; thioguanine; thiotepa; tiazofurin; tirapazamine; toremifene citrate; trestolone acetate; triciribine phosphate; trimetrexate; trimetrexate glucuronate; triptorelin; tubulozole hydrochloride; uracil mustard; uredepa; vapreotide; verteporfin; vinblastine sulfate; vincristine sulfate; vindesine; vindesine sulfate; vinepidine sulfate; vinglycinate sulfate; vinleurosine sulfate; vinorelbine tartrate; vinrosidine sulfate; vinzolidine sulfate; vorozole; zeniplatin; zinostatin; zorubicin hydrochloride. Other anti-cancer drugs include, but are not limited to: 20-epi-1,25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein-1;

antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstaurosporine; beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate; bropirimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; canarypox IL-2; capecitabine; carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetrorelix; chlorlns; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentanthraquinones; cycloplatam; cypemycin; cytarabine ocfosfate; cytolytic factor; cytostatin; dacliximab; decitabine; dehydrodidemnin B; deslorelin; dexamethasone; dexifosfamide; dexrazoxane; dexverapamil; diaziquone; didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; dihydrotaxol, 9-; dioxamycin; diphenyl spiromustine; docetaxel; docosanol; dolasetron; doxifluridine; droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflornithine; elemene; emitefur; epirubicin; epristeride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelastine; fluasterone; fludarabine; fluorodaunorunicin hydrochloride; forfenimex; formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; ilmofosine; ilomastat; imidazoacridones; imiquimod; immunostimulant peptides; insulin-like growth factor-1 receptor inhibitor; interferon agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol, 4-; iroplact; irsogladine; isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide+estrogen+progesterone; leuprorelin; levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds;

lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; lovastatin; loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A; marimastat; masoprocol; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mismatched double stranded RNA; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim; monoclonal antibody, human chorionic gonadotrophin; monophosphoryl lipid A+myobacterium cell wall sk; mopidamol; multiple drug resistance gene inhibitor; multiple tumor suppressor 1-based therapy; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone+pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic acid; neutral endopeptidase; nilutamide; nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullyn; O6-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxaunomycin; paclitaxel; paclitaxel analogues; paclitaxel derivatives; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentrozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiromycin; prednisone; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylene conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rogletimide; rohitukine; romurtide; roquinimex; rubiginone B1; ruboxyl; safingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; signal transduction modulators; single chain antigen binding protein; sizofiran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1;

squalamine; stem cell inhibitor; stem-cell division inhibitors; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; synthetic glycosaminoglycans; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; temozolomide; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene bichloride; topsentin; toremifene; totipotent stem cell factor; translation inhibitors; tretinoin; triacetyluridine; triciribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; vector system, erythrocyte gene therapy; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; and zinostatin stimalamer.

The compounds of the present invention and the other therapeutic agent can act additively or, more preferably, synergistically. In a preferred embodiment, a composition comprising a compounds of the present invention is administered concurrently with the administration of another therapeutic agent, which can be part of the same composition or in a different composition from that comprising the compounds of the present invention. In another embodiment, a composition comprising the compounds of the present invention is administered prior to or subsequent to administration of another therapeutic agent.

The compounds of the present invention when administered, e.g., via the oral, parenteral or topical routes to mammals, can be in a dosage in the range of about 0.01 mg/kg to about 3000 mg/kg body weight of the patient per day, preferably about 0.01 mg/kg to about 1000 mg/kg body weight per day administered singly or as a divided dose. However, variations will necessarily occur depending upon the weight and physical condition (e.g., hepatic and renal function) of the subject being treated, the affliction to be treated, the severity of the symptoms, the route of administration, the frequency of the dosage interval, the presence of any deleterious side-effects, and the particular compound utilized, among other things.

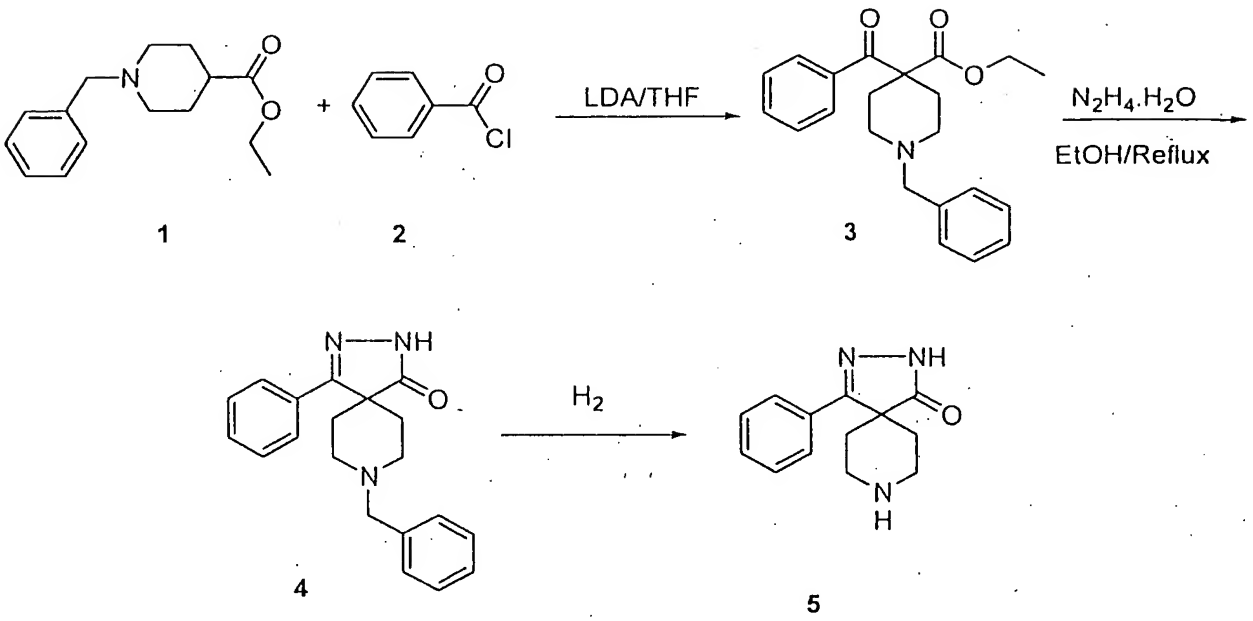
The compounds of the present invention preferably have a binding affinity K_i for the human ORL-1 receptor of about 500 nM or less; 100 nM or less; 50 nM or less; 20 nM or less or 5 nM or less. The binding affinity K_i can be measured by one skilled in the art by an assay utilizing membranes from recombinant HEK-293 cells expressing the human opioid receptor-like receptor (ORL-1) as described below.

The following examples illustrate various aspects of the present invention, and are

not to be construed to limit the claims in any manner whatsoever.

EXAMPLE 1

Synthesis of spirocyclic head groups.



1 2 3 4 5

Procedure:

To a solution of freshly prepared LDA in THF (1.1 eq) at –40°C was added a solution of 1 (1 eq) in THF. The reaction mixture was allowed to warm to RT and stir for 1 hr. After cooling to –20°C, a solution of benzoyl chloride (2, 1.2 eq) in THF was added dropwise. After stirring at –20°C for 1 hr and at RT for 16 hr, the reaction mixture was poured into water and extracted with ethyl acetate. The organic extracts were washed with saturated ammonium chloride, brine, dried over $MgSO_4$, filtered and the solvent evaporated to give crude 3 as an oil, which was used without purification in the next step.
^{1}H-NMR ($CDCl_3$): d 1.08 (t, 3H), 2.28 (t, 4H), 2.43 (m, 2H), 2.54 (m, 2H), 3.46 (s, 2H), 4.13 (q, 2H), 7.21-7.31 (m, 5H), 7.39 (m, 2H), 7.49 (m, 1H), 7.79 (m, 2H).

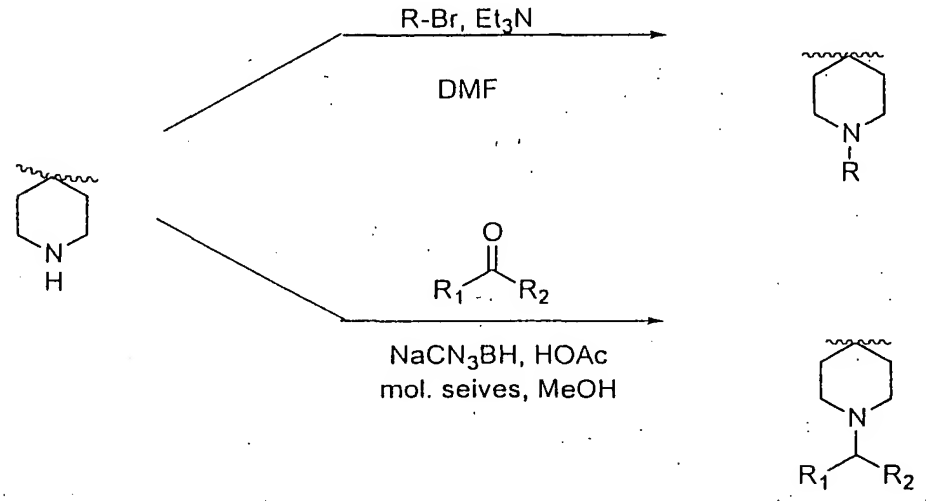
To a solution of 3 (1 eq) in ethanol was added hydrazine hydrate (3 eq). After refluxing for 12 hr, the reaction mixture was cooled to RT and the crude product filtered. The solid was recrystalized from ethanol to give 4 as a white solid.
^{1}H-NMR (DMSO): d 1.67 (d, 2H), 2.23 (dt, 2H), 2.62 (dd, 2H), 2.83 (dt, 2H), 3.56 (s, 2H), 7.25 (m, 1H), 7.35 (m, 4H), 7.50 (m, 3H), 7.78 (m, 2H).

Compound 4 (1 eq) and $Pd(OH)_2$ (0.2 eq) in methanol was hydrogenated at RT and 50 psi of hydrogen for 20 hr. Filtration and evaporation gave crude 5. Recrystalization from ethanol gave pure 5 as a white solid.

^{1}H-NMR (DMSO): d 1.50 (d, 2H), 2.12 (m, 2H), 2.73 (m, 2H), 3.28 (m, 2H), 7.45 (m, 3H), 7.86 (d, 2H).

EXAMPLE 2
ATTACHMENT OF TAIL GROUPS

Tail groups were attached to the head groups according to the following procedures:



General procedure for alkylation:

To a solution of the amine (1 eq) and triethylamine (1 eq) in dimethylformamide, was added 1 eq of alkyl bromide or chloride in one portion. The mixture was stirred and heated at 80°C over night. TLC indicated the reaction was complete. The reaction was quenched by the addition of water followed by 1 N NaOH to pH 10. The mixture was extracted 2x with Et_2O. The combined organic extracts were dried over potassium carbonate and the solvent evaporated, followed by chromatography to give the pure product.

General procedure for reductive amination:

To a mixture of ketone or aldehyde (1 eq), amine (1 eq), and acetic acid (1 eq) in methanol, was added sodium cyanoborohydride (1.4 eq) in one portion. The mixture was stirred over night at room temperature. TLC indicated the reaction was complete. The reaction was quenched by the addition of water followed by 1 N NaOH to pH 10. The mixture was extracted 2x with Et_2O. The combined organic extracts were dried over

potassium carbonate and the solvent evaporated, followed by chromatography to give the pure product.

The following compounds were prepared by attaching the tail groups using the general procedures described:

8-(benzyl)-1-phenyl-2,3,8-triazospiro[4.5]decan-4-one
MS: m/z 342.2 (M+Na)
^{1}H-NMR (DMSO): d 1.67 (d, 2H), 2.23 (dt, 2H), 2.62 (dd, 2H), 2.83 (dt, 2H), 3.56 (s, 2H), 7.25 (m, 1H), 7.35 (m, 4H), 7.50 (m, 3H), 7.78 (m, 2H).

8-[(naphth-2-yl-methyl)]-1-phenyl-2,3,8-triazospiro[4.5]decan-4-one
LC: 97.7%
MS: m/z 370.6 (M+1)
^{1}H-NMR ($CDCl_3$): d 1.80 (b, 2H), 2.50 (m, 2H), 2.80 (b, 2H), 2.03 (t, 2H), 3.75 (s, 2H), 7.50 (m, 5H), 7.60 (d, 1H), 7.80 (m, 6H), 8.42 (b, 1H).

8-(*p*-phenylbenzyl)-1-phenyl-2,3,8-triazospiro[4.5]decan-4-one
LC: 90.1%
MS: m/z 396.6 (M+1)
^{1}H-NMR ($CDCl_3$): d 1.80 (b, 2H), 2.51 (m, 2H), 2.80 (b, 2H), 3.02 (m, 2H), 3.75 (s, 2H), 7.35-7.70 (m, 12H), 7.85 (b, 2H), 8.50 (b, 1H).

8-(10,11-Dihydro-5H-dibenzo[a,d]-cyclohepten-5-yl)-1-phenyl-2,3,8-triazospiro[4.5]decan-4-one
LC: 100%
MS: m/z 444.2 (M+Na).
^{1}H-NMR ($CDCl_3$): d 1.75 (b, 2H), 2.35 (m, 2H), 2.61 (b, 2H), 2.85 (m, 4H), 4.11 (m, 2H), 4.20 (s, 1H), 7.10-7.28 (m, 8H), 7.45 (m, 3H), 7.85 (m, 2H), 8.5 (s, 1H).

8-[4,4-Bis(4-fluorophenyl)butyl]-1-phenyl-2,3,8-triazospiro[4.5]decan-4-one
LC: 96.9%
MS: m/z
^{1}H-NMR ($CDCl_3$): d 0.75-2.90 (m, 10H), 3.60 (m, 2H), 3.80 (m, 1H), 3.90 (m, 1H), 4.55 (m, 1H), 6.90-7.50 (m, 11H), 7.80 (b, 2H), 8.45 (b, 1H).

8-(3,3-Bis(phenyl)propyl)-1-phenyl-2,3,8-triazospiro[4.5]decan-4-one
LC: 100%

MS: m/z 424.2 (M+1)
^{1}H-NMR ($CDCl_3$): d 1.80 (b, 2H), 2.35 (m, 2H), 2.50 (m, 4H), 2.78 (b, 2H), 2.95 (m, 2H), 4.05 (t, 1H), 7.20 (m, 2H), 7.30 (m, 8H), 7.45 (m, 3H), 7.85 (b, 2H), 8.70 (b, 1H).

8-(*p*-benzyloxybenzyl)-1-phenyl-2,3,8-triazospiro[4.5]decan-4-one
LC: 97.6%
MS: m/z 426.2
^{1}H-NMR ($CDCl_3$): d 1.80 (b, 2H), 2.45 (dt, 2H), 2.80 (b, 2H), 2.95 (m, 2H), 3.60 (s, 2H), 5.10 (s, 2H), 6.95 (d, 2H), 7.30-7.50 (m, 10H), 7.88 (m,2H), 8.71 (s,1H).

8-(1,2,3,4-tetrahydro-2-naphthyl)-1-phenyl-2,3,8-triazospiro[4.5]decan-4-one
LC: 95.3%
MS: m/z 360.2 (M+1)
^{1}H-NMR ($CDCl_3$): d 1.85-1.90 (m, 3H), 2.42 (b, 1H), 2.85-3.15 (m, 6H), 3.20 (b, 2H), 3.40 (m, 2H), 3.75 (m, 1H), 7.10-7.20 (m, 4H), 7.50 (m, 3H), 8.00 (d, 2H).

8-(4-propylcyclohexyl)-1-phenyl-2,3,8-triazospiro[4.5]decan-4-one
LC: 100%
MS: m/z 354.2 (M+1)
^{1}H-NMR ($CDCl_3$): d 1.95 (t, 3H), 1.35 (m, 6H), 1.60 (m, 2H), 1.80 (m, 3H), 1.95 (d, 4H) 2.25 (d, 1H), 3.05 (t, 3H), 3.30 (d, 2H), 3.8 (q. 2H), 7.50 (t, 1H), 7.60 (m, 2H), 8.00 (d, 2H).

8-(5-methylhex-2-yl)-1-phenyl-2,3,8-triazospiro[4.5]decan-4-one
LC: 100%
MS: m/z 328.2 (M+1)
^{1}H-NMR ($CDCl_3$): d 0.9-1.65 (m, 12H), 2.00 (bd, 4H), 2.05-2.30 (m, 5H), 3.95 (t, 2H), 7.50 (t, 1H), 7.60 (t, 2H), 8.02 (d, 2H).

8-norbornyl-1-phenyl-2,3,8-triazospiro[4.5]decan-4-one
MS: m/z 324.2 (M+1)
^{1}H-NMR ($CDCl_3$): d 0.80-3.90 (m, 16H), 4.20 (m, 2H), 4.85 (b, 1H), 7.40-7.62 (m, 3H), 8.05 (m, 2H), 8,75 (b, 1H).

8-(decahydro-2-naphthyl)-1-phenyl-2,3,8-triazospiro[4.5]decan-4-one
LC: 100%
MS: m/z 366.2 (M+1)
^{1}H-NMR ($CDCl_3$): d 0.95-2.15 (m, 17H), 2.30 (m, 1H), 3.10 (m, 3H), 3.35 (m, 2H), 3.95 (m, 2H), 7.55 (t, 1H), 7.65 (t, 2H), 8.02 (d, 2H).

8-(cyclooctylmethyl)-1-phenyl-2,3,8-triazospiro[4.5]decan-4-one
LC: 100%
MS: m/z 340.2 (M+1)
^{1}H-NMR ($CDCl_3$): d 1.40-2.25 (m, 16H), 3.10 (m, 2H), 3.20 (b, 2H), 3.38 (m, 1H),4.02 (m, 2H), 7.50 (t, 1H), 7.60 (t, 2H), 8.02 (m, 2H).

8-[4-(2-propyl)-cyclohexyl]-1-phenyl-2,3,8-triazospiro[4.5]decan-4-one
LC: 100%
MS: m/z 354.2 (M+1)
^{1}H-NMR ($CDCl_3$): d 0.9 (m, 6H), 1.45-1.65 (m, 3H), 1.78 (m, 2H), 2.00 (b, 6H), 2.30 (d, 1H), 3.10 (m, 3H), 3.30 (t, 2H), 3.95 (q, 2H), 7.50 (t, 1H), 7.60 (t, 2H), 8.00 (m, 2H).

8-(1,3-dihydroinden-2-yl)-1-phenyl-2,3,8-triazospiro[4.5]decan-4-one
LC: 100%
MS: m/z 346.1 (M+1)
^{1}H-NMR ($CDCl_3$): d 1.90-3.80 (m, 12H), 4.25 (m, 1H), 7.20 –7.70 (m, 8H), 7.95 (d, 1H).

8-(cyclooctylmethyl)-1-phenyl-2,3,8-triazospiro[4.5]decan-4-one
LC: 92.9%
MS: m/z 354.6 (M+1)
^{1}H-NMR (MeOH): d 1.40-1.80 (m, 14H), 2.00 (b, 2H), 2.10 (m, 1H), 2.60 (m, 2H), 2.90 (m, 2H), 3.40 (m, 2H), 3.70 (m, 2H), 7.50 (m, 3H), 7.80

8-(acenaphthen-9-yl)-1-phenyl-2,3,8-triazospiro[4.5]decan-4-one
LC: 100%
MS: *m/z* 382.2 (M+1)
^{1}H-NMR ($CDCl_3$): 1.69 (dd, 1H), 1.72 (dd, 1H), 2.36-2.44 (m, 2H), 2.52-2.60 (ddd, 1H), 2.83 (brd, 1H), 3.17-3.24 (m, 1H), 3.30-3.44 (m, 2H), 3.60-3.65 (m, 1H) 5.01 (dd, 1H), 7.31 (d, 1H), 7.45-7.49 (m, 4H), 7.52-7.57 (m, 2H), 7.62-7.64 (d, 1H), 7.69-7.71 (m, 1H), 7.86-7.88 (m, 2H), 8.42 (s, 1H)

Other compounds within the scope of formula (I) or (IA) of the present invention can be synthesized by analogous techniques.

EXAMPLE 3

Nociceptin affinity at the ORL1 receptor for preferred compounds was obtained using the following assay:

Membranes from recombinant HEK-293 cells expressing the human opioid receptor-like receptor (ORL-1) (Receptor Biology) were prepared by lysing cells in ice-cold hypotonic buffer (2.5 mM $MgCl_2$, 50 mM HEPES, pH 7.4) (10 ml/10 cm dish) followed by homogenization with a tissue grinder/teflon pestle. Membranes were collected by centrifugation at 30,000 x g for 15 min at 4°C and pellets resuspended in hypotonic buffer to a final concentration of 1-3 mg/ml. Protein concentrations were determined using the BioRad protein assay reagent with bovine serum albumen as standard. Aliquots of the ORL-1 receptor membranes were stored at –80°C.

Functional SGTPgS binding assays were conducted as follows. ORL-1 membrane solution was prepared by sequentially adding final concentrations of 0.066 mg/ml ORL-1 membrane protein, 10 mg/ml saponin, 3 mM GDP and 0.20 nM [^{35}S]GTPgS to binding buffer (100 mM NaCl, 10 mM $MgCl_2$, 20 mM HEPES, pH 7.4) on ice. The prepared membrane solution (190 ml/well) was transferred to 96-shallow well polypropylene plates containing 10 ml of 20x concentrated stock solutions of agonist prepared in DMSO. Plates were incubated for 30 min at room temperature with shaking. Reactions were terminated by rapid filtration onto 96-well Unifilter GF/B filter plates (Packard) using a 96-well tissue harvester (Brandel) and followed by three filtration washes with 200 ml ice-cold binding buffer (10 mM NaH_2PO_4, 10 mM Na_2HPO_4, pH 7.4). Filter plates were subsequently dried at 50°C for 2-3 hours. Fifty ml/well scintillation cocktail (BetaScint; Wallac) was added and plates were counted in a Packard Top-Count for 1 min/well.

Data was analyzed using the curve fitting functions in GraphPad PRISMÔ, v. 3.0 and the results are set forth in table 1 below:

TABLE 1	
Nociceptin Affinity	
Compound	calc K_i (nM)
8-(4-propylcyclohexyl)-1-phenyl-2,3,8-triazospiro[4.5]decan-4-one	29.7
8-(5-methylhex-2-yl)-1-phenyl-2,3,8-triazospiro[4.5]decan-4-one	11.5
8-norbornyl-1-phenyl-2,3,8-triazospiro[4.5]decan-4-one	897
8-(decahydro-2-naphthyl)-1-phenyl-2,3,8-triazospiro[4.5]decan-4-one	1.1
8-(cyclooctylmethyl)-1-phenyl-2,3,8-triazospiro[4.5]decan-4-one	8.1
8-(1,2,3,4-tetrahydro-2-naphthyl)-1-phenyl-2,3,8-triazospiro[4.5]decan-4-one	52.3
8-[4-(2-propyl)-cyclohexyl]-1-phenyl-2,3,8-triazospiro[4.5]decan-4-one	1.5
8-(1,3-dihydroinden-2-yl)-1-phenyl-2,3,8-triazospiro[4.5]decan-4-one	43
8-[(naphth-2-yl-methyl)]-1-phenyl-2,3,8-triazospiro[4.5]decan-4-one	402
8-(*p*-phenylbenzyl)-1-phenyl-2,3,8-triazospiro[4.5]decan-4-one	7171
8-[4,4-Bis(4-fluorophenyl)butyl]-1-phenyl-2,3,8-triazospiro[4.5]decan-4-one	2589
8-(benzyl)-1-phenyl-2,3,8-triazospiro[4.5]decan-4-one	293
8-(10,11-Dihydro-5H-dibenzo[a,d]-cyclohepten-5-yl)-1-phenyl-2,3,8-triazospiro[4.5]decan-4-one	282
8-(3,3-Bis(phenyl)propyl)-1-phenyl-2,3,8-triazospiro[4.5]decan-4-one	75
8-(*p*-benzyloxybenzyl)-1-phenyl-2,3,8-triazospiro[4.5]decan-4-one	138
8-(cyclooctylmethyl)-1-phenyl-2,3,8-triazospiro[4.5]decan-4-one	61
8-(acenaphthen-9-yl)-1-phenyl-2,3,8-triazospiro[4.5]decan-4-one	.06

Example 5

Affinity at the μ receptor for compounds was obtained according to the following assay:

Mu opioid receptor membrane solution was prepared by sequentially adding final concentrations of 0.075 μg/μl of the desired membrane protein, 10 μg/ml saponin, 3 μM GDP and 0.20 nM [^{35}S]GTPγS to binding buffer (100 mM NaCl, 10 mM $MgCl_2$, 20 mM HEPES, pH 7.4) on ice. The prepared membrane solution (190 μl/well) was transferred to 96-shallow well polypropylene plates containing 10 μl of 20x concentrated stock solutions of agonist prepared in DMSO. Plates were incubated for 30 min at room temperature with shaking. Reactions were terminated by rapid filtration onto 96-well Unifilter GF/B filter plates (Packard) using a 96-well tissue harvester (Brandel) and followed by three filtration washes

with 200 µl ice-cold binding buffer (10 mM NaH_2PO_4, 10 mM Na_2HPO_4, pH 7.4). Filter plates were subsequently dried at 50° C for 2-3 hours. Fifty µl/well scintillation cocktail (MicroScint20, Packard) was added and plates were counted in a Packard Top-Count for 1 min/well.

Data were analyzed using the curve fitting functions in GraphPad PRISM ™, v. 3.0 and the results for several compounds are set forth in table 2 below:

TABLE 2

Mu Receptor Affinity

Compound	calc K_i (nM)
8-(1,2,3,4-tetrahydro-2-naphthyl)-1-phenyl-2,3,8-triazospiro[4.5]decan-4-one	115
8-[(naphth-2-yl-methyl)]-1-phenyl-2,3,8-triazospiro[4.5]decan-4-one	84
8-(benzyl)-1-phenyl-2,3,8-triazospiro[4.5]decan-4-one	56
8-(cyclooctylmethyl)-1-phenyl-2,3,8-triazospiro[4.5]decan-4-one	191